Clinician approach to cardiopulmonary exercise testing for exercise prescription in patients at risk of and with cardiovascular disease

Peer-reviewed author version

D'Ascenzi, Flavio; Cavigli, Luna; Pagliaro, Antonio; Focardi, Marta; Valente, Serafina; Cameli, Matteo; Mandoli, Giulia Elena; Mueller, Stephan; DENDALE, Paul; Piepoli, Massimo; Wilhelm, Matthias; Halle, Martin; Bonifazi, Marco & HANSEN, Dominique (2022) Clinician approach to cardiopulmonary exercise testing for exercise prescription in patients at risk of and with cardiovascular disease. In: British journal of sports medicine, 56 (20) , p. 1180+-.

DOI: 10.1136/bjsports-2021-105261
Handle: http://hdl.handle.net/1942/37601

A clinician approach to cardiopulmonary exercise testing and exercise prescription: treat exercise as the powerful medicine it is

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ABSTRACT

Exercise training is highly recommended in current guidelines on primary and secondary prevention of cardiovascular disease (CVD). This is based on the cardiovascular benefits of physical activity and structured exercise, ranging from improving the quality of life to reducing CVD and overall mortality. A tailored approach based on the patient's personal and clinical characteristics represents a cornerstone for the benefits of exercise prescription. In this regard, the use of cardiopulmonary exercise testing is well-established for risk stratification, quantification of cardiorespiratory fitness and ventilatory thresholds for a tailored, personalized exercise prescription. The aim of this paper is to provide practical guidance to clinicians on how to use data from cardiopulmonary exercise testing towards personalized exercise prescriptions for patients with CVD.

INTRODUCTION

In the primary and secondary prevention of cardiovascular disease (CVD), structured exercise training combined with a recommended level of habitual physical activity is a cornerstone, next to smoking cessation, healthy nutrition, adequate coping skills towards psychosocial stress and adherence to guideline-directed medical therapies(1, 2). As a result, every year, millions of individuals at risk for or with established CVD on a global scale receive the advice to increase their habitual physical activity level and minimize the time spent sitting and exercising in a structured manner. For the latter, clinicians should clearly specify the frequency, intensity, time, and type (FITT) of exercise(3).

In this endeavour, clinicians should rely on objective outcomes from clinical assessments and personalize the exercise prescription accordingly. Unfortunately, this remains challenging to many clinicians prescribing exercise in CVD (risk) patients(4-6). In particular, how to properly determine exercise intensity (EI) remains a highly debated topic. Due to the discrepancies in the guideline-derived EI domains(7-11), it seems fair to conclude that patient-specific EI parameters should be used in clinical practice. Indeed, in the latest position statement of the European Association of Preventive Cardiology (EAPC) and their Core Curriculum for Preventive Cardiology, it is concluded that the ventilatory thresholds, derived from cardiopulmonary exercise testing (CPET), should primarily be used to determine the EI, instead of the primary focus on proxies from maximal outcomes during exercise testing (e.g. peak heart rate, workload or oxygen uptake)(12) or subjective assessments (e.g. Borg ratings of perceived exertion)(13), highlighting the importance of CPET for diagnosis, risk stratification and exercise prescription as a core entrustable professional activity(14).

This manuscript aims to provide an overview of CPET indications and methodology, parameters and interpretation, and how to adjust exercise prescription from CPET outcomes to the patient's phenotype.

Cardiopulmonary exercise testing: indications and methodology

CPET combines the integrated analysis of ventilation (VE), oxygen saturation, oxygen consumption (VO_2) and carbon dioxide production (VCO_2) with parameters commonly evaluated during the incremental exercise ECG testing, such as power output (watt), heart rate (HR), blood pressure (BP), ECG changes, and subjective symptoms(15), providing a comprehensive vision of involved mechanisms in the transport and use of O_2 during physical exercise(16).

The measurement of gas exchanges during exercise has become increasingly widespread in clinical practice (although this remains to be achieved in some regions/countries), and the potential applications of CPET range from functional capacity estimation to prognostic stratification, from the evaluation of the effectiveness of a treatment to the tailored prescription of physical exercise, from the assessment of the indication of a patient to heart transplantation to the evaluation of peri- and post-operative surgical risk and of valvular heart disease(15-17). The integrated analysis of the cardiovascular, respiratory, and metabolic responses to exercise allows both evaluating the grade of any functional limitation and gaining information about the pathophysiology of exercise itself, with a specific value on the causes of functional limitation and symptoms relied on by the patient(17), synthetically attributable to cardiac, ventilatory, vascular, pulmonary or peripheral problems.

Methodologically, CPET includes an ECG registration system and a VE and exhaled gas (VO_2 and VCO_2) measurement system, which can be done breath-by-breath, most frequently used in clinical practice, or the mixing chamber (every 30 seconds)(18). The test can be conducted on a cycle

ergometer or a treadmill. Differences between both challenges are that treadmill CPET has a higher HR and greater energy expenditure, which results in VO_{2peak} values 10-15% higher than the cycle ergometer(15) (see supplementary table 1 for the difference between treadmill vs cycle ergometer). Notably, the type of exercise protocol used significantly affect the result of CPET evaluation(19). Protocols defined "ramp" (slight load increase in a short time, with gradual increase of watts during one minute) should be preferred to scalar protocols “stepped” because the former yields improved measurements of ventilatory thresholds (VTs), may determine exercise capacity continuously and also yields functional capacity more accurately than stepwise protocols(19). In contrast, stepwise protocols are used for lactate testing during exercise, as an equilibrium of lactate is only reached after 3-4 min intervals (lactate analysis at the end of each step). Different standardized exercise stepwise protocols are available: Bruce, modified Bruce, Cornell, Naughton, Åstrand(20). Several ramp grades are commonly used for patients, with 10 W/min and 15 W/min the most popular(15). The choice of ramp protocol steepness should be tailored to the subject’s estimated exercise tolerance to obtain analyzable and reproducible results and aiming at test duration ranging between 8 and 12 min(15); if the load increase is excessive or insufficient, the peak is reached too quickly or too late, and the final results will tend to underestimate the actual maximal exercise capacity (VO_2peak or VO_2max) of the patient(18) (see supplementary Table 1).

The interpretation of cardiopulmonary exercise testing

The Nine-Panel Plot

To date, the most used analysis scheme shows nine different graphs (Figure 1). This format was introduced by Wasserman in 1986 and optimized up to the most recent versions(21).

The nine-panel plot can be schematized as it follows:

- *Panel 1*: This shows gas kinetic analysis (VO_2, VCO_2) over time. As the work rate (WR) increases, there is a continuous linear increase in VO_2. When formatted appropriately (ratio of $\dot{V}O_2$ to WR, of at least 10mL/min to 1 watt), $\dot{V}O_2$ and WR should show a parallel increase until peak exercise (or shortly before). $\dot{V}CO_2$ shows a linear increase until the first ventilatory threshold (VT_1) is reached and disproportionally increases thereafter.
- *Panel 2*: This shows HR and oxygen pulse (VO_2/HR) over time, an indicator of cardiac performance and systolic output. According to the Fick principle, the oxygen pulse is the product of stroke volume and the difference in the arterio-venous oxygen content. A pattern of flattening or declining cannot be explained by a change in the extraction and is therefore suggestive of altered stroke volume due to left or right ventricular dysfunction (e.g. exercise-induced ischemia)
- *Panel 3*: This shows HR and VCO_2 plotted over VO_2. The slope of VCO_2 over VO_2 is less or equal to 1 until VT_1 is reached. Above the VT_1, VCO_2 increases at a higher rate than VO_2 and causes a change in the slope (>1), the incline depending on the effectiveness of the lactic acidosis buffering systems.
- *Panel 4*: This shows the ventilatory equivalent for VO_2 and VCO_2 plotted over time. For calculating ventilatory equivalents (VE/VO_2, VE/VCO_2 or EqO_2, $EqCO_2$), the additional dead space from the face mask is subtracted from ventilation, e.g. [(VE - dead space * breathing frequency) / VO_2]. Under physiological conditions, ventilatory equivalents decrease until they reach a nadir value at VT_1 for VE/VO_2 and the second ventilatory threshold (VT_2) for VE/VCO_2 (traditionally identified with respiratory compensation, also sometimes coined as the 'respiratory compensation point').
- *Panel 5:* This shows the ventilation trend during a progressive workload, with a change in the slope above VT_1 due to the increase in the respiratory drive, following the rise in circulatory

CO_2. This panel also shows a change in slope at VT_2 due to the saturation of buffer systems, thus leading to acidosis (lactate accumulation) and further stimulation of hyperventilation.

- *Panel 6*: This shows the relationship between VE and VCO_2 and measures ventilatory CO_2 elimination efficiency.
- *Panel 7*: This shows the analysis of partial end-tidal pressures of O_2 ($PetO_2$) and CO_2 ($PetCO_2$), providing information about ventilation/perfusion mismatch.
- *Panel 8:* shows the respiratory exchange ratio (RER) as a function of time. RER represents the VCO_2 to VO_2 ratio, proper to obtain information on the energy expenditure and the relative contribution of the individual substrates (carbohydrates and fatty acids). The RER (measured at the mouth) equals the respiratory quotient (RQ, measured in the mitochondria) at rest and during low-intensity constant-load exercise. At the beginning of the exercise, RER is between 0.7 and 0.9. While the RQ cannot increase above 1.0 (upper limit of aerobic energy metabolism), the RER increases beyond 1.1 at peak effort due to additional CO_2 production and hyperventilation during anaerobic metabolism.
- *Panel 9*: This shows tidal volume (TV) as a function of VE.

Ventilatory Threshold

Definition of ventilatory threshold

The concept of VTs is related to alterations in energy metabolism during exercise. From a physiological point of view, the model of lactate metabolism during incremental exercise is divided into three different phases and two points of intersection (Figure 2)(22, 23):

- *Phase I*: A linear increase in VO_2, VCO_2 and VE is observed; energy production is almost exclusively aerobic with efficient ventilation and great O2 tissue extraction leading to low EqO2 and PetO2, without a significant blood lactate increase until the VT_1 is reached.
- *Phase II*: as EI increases above VT_1, lactate production increases faster than the metabolizing capacity in muscle cells, resulting in a modest, progressive blood lactate accumulation. However, the resulting increase in hydrogen ions (H^+) is successfully buffered by bicarbonate (HCO_3^-), resulting in an increased production of CO_2, the so-called excess CO_2. The higher circulatory level of CO_2 stimulates central receptors and peripheral chemoreceptors, leading to a steeper increase of VE to adequately eliminate the excess CO_2, resulting in a nadir of $EqCO_2$ and a continuous rise or plateau of $PetCO_2$ in exhaled air. During this phase, buffer systems provide a condition near constant load until the VT_2 is reached.
- *Phase III*: The workload increase above the VT_2 causes a rise in lactate production that exceeds the rate at which it can be broken down. Lactate concentration in the blood increases exponentially. Bicarbonate buffering is no more sufficient to break down the H+ accumulation leading to an increased ventilatory drive, the so-called respiratory compensation. $EqCO_2$ rises, and a drop in $PetCO_2$ occurs. However, hyperventilation is not enough to compensate for the increase in H^+ and acidosis until peak exercise.

Schematically, it is possible to consider the VT_1 as the limit that defines the transition from mild to moderate EI. In contrast, the VT_2 represents the transition from heavy to very heavy EI.

The VT_1 demarcates the upper limit of a range of EI that can be accomplished almost entirely aerobically. While work rates below VT_1 can be sustained for an exceptionally long time, a progressive increase in WR above VT_1 is associated with a progressive decrease in exercise duration. VT_1 occurs at about 40-60% of VO_{2max} predicted in normal sedentary individuals, with a variable

range of normal values in different studies(24). Besides its importance for obtaining prognostic information in heart failure (HF) patients, VTs determination can be helpful as an indicator of the fitness level, a tailored exercise prescription, and monitor the effects of a training program(25).

For the assessment of lactate metabolism during exercise, two different methods can be used: (I) direct measurement of blood lactate, (II) non-invasive indirect determination through gas exchanges and ventilation analysis. Therefore, even if the terms "ventilatory threshold" and "lactate threshold" are not interchangeable, they are closely related. However, the nomenclature is not uniform and sometimes even confusing. In 1964, Wasserman and Mcllroy introduced the concept of "anaerobic metabolism threshold", defined as the EI that causes an increase in RER, accompanied by a decrease in arterial blood bicarbonate and by the onset of metabolic acidosis(26). This threshold corresponds approximately to VT_1; however, the term "anaerobic threshold" as a designation of VT_1 became of everyday use after 1973(27). The same word "anaerobic threshold" was also used by Skinner et al. in the three-phase model to describe the transition from phase II to phase III, corresponding to VT_2(23). In the same model, the transition point from phase I to II was referred to as "aerobic threshold", and afterwards, several authors have embraced this classification(23). Therefore, the absence of a uniform nomenclature has caused significant contradictions in the scientific community and can be partially explained by the inability of the "aerobiosis/anaerobiosis" binomen to fully reflect the physiology of exercise. During exercise, energy production is not determined by an entirely aerobic or anaerobic mechanism(28). Moreover, the increase in blood lactate occurs regardless of peripheral O_2 supply. To overcome these contradictions, we have adopted the terms "first" and "second" VT to identify the changes in slope in lactic acid kinetics, focusing the attention on the presence of changes in metabolism rather than on the metabolism typology(29).

Determination of the ventilatory thresholds

The invasive determination of thresholds relies on the blood lactate concentrations, which does not rise linearly compared with WR, but shows the first increase concurrently with the VT_1, reaching values higher than 2 mmol/l, equivalent to the "first VT"(22). As WR increases above the VT_1, lactate production equals maximal lactate clearance capacity, reaching a point equivalent to the VT_2 and an approximate blood lactate value of 4 mmol/l ("second VT")(22, 30). However, this method does not consider the interindividual variability in blood lactate concentrations that may deviate from the abovementioned values, especially for the VT_2(31).

The non-invasive VTs determination is based on the analysis and integration of data derived from some of the nine panels. The most used methods for VT_1 determination are characterized by the following points (Figure 3)(22):

- A change in the slope of VCO_2 versus VO_2 ratio (V-slope method, panel 3) from an increase with a slope less than or equal to 1 to a slope greater than 1 (the gold standard for detection of VT_1);
- The nadir of the first increase in VE/VO_2, without a simultaneous increase in VE/VCO_2 (panel 4);
- The nadir of $PetO_2$, while $PetCO_2$ remains constant or is increasing (panel 6).

The following points define VT_2 (figure 3)(22):

- The inflexion of VE versus WR (panel 5);
- The nadir of VE/VCO_2 increase (panel 4);
- The inflexion of VE over VCO_2 (panel 6);
- The Zenit and deflection point of $PetCO_2$ (panel 7).

VTs determination may be challenging in some cases, particularly in HF and elderly patients (VT_1/VT_2 identifiable in 76%/54% of elderly CVD patients)(6). In HF patients, a VO_{2peak} decrease and a VE/VCO_2 increase are typically found. Early lactic acid accumulation often leads to inaccurate identification of the transition point from phase I to phase II and leads to hyperventilation(32). VE/VO_2 in such cases does not show a clear nadir and tends to increase progressively(22). Moreover, albeit anaerobic metabolism has been reached, in a part of HF patients, VT_1 cannot be identified regardless of the method used. This happens in ~10% of HF patients, more specifically in patients with severe HF and is likely due to inhomogeneity of muscle O_2 delivery and muscle function(33). Furthermore, in HF patients, an abnormal ventilatory response can be observed. This response is characterized by ventilatory oscillations, a phenomenon characterized by cyclical breath fluctuations and present in about 20% of patients with HF(34), making VTs correct determination impossible. Furthermore, the possibility of identifying the VT_2 depends to a large extent on the gain of the chemoreceptive response to metabolic acidosis, which can vary among subjects/patients, thereby making the VT_2 identification potentially difficult (22, 25). Notably, the absence of identifiable VTs, regardless of absolute values of VO2 or WR, is a poor prognostic factor in HF (35). See supplementary material for case presentations of typical HF-related alterations during CPET.

One main limitation of using VTs to prescribe exercise is that manual analysis is time-consuming and is affected by a non-negligible intra- and inter-observer variability(32). However, if highly experienced clinicians determine VTs, the coefficient of variation is relatively low(36-39). Therefore, physicians must know the importance of obtaining VTs during CPET and that training is critical to interpreting CPET data appropriately.

On the other hand, when aerobic EI is prescribed using indices of peak effort (e.g. % VO_{2peak}), one of the main limitations is represented by the fact that not all cardiac patients can achieve a near-maximal effort during CPET and, therefore, this may have a relevant impact on the determination

of the appropriate EI. Conversely, VT_1 and VT_2 are effort-independent and do not require complete exhaustion. Although CPET gives the unique opportunity to define VTs for each patient, the % of VO_{2peak} and % of HR $_{max}$ are frequently used to prescribe exercise. Unfortunately, the HR recommendations-based parameters of EI may not correspond to the ventilatory threshold-based intensity of exercise and may misclassify the proper level of EI(11), particularly in cardiac patients under beta-blocker therapy (e.g. patients with ischemic heart disease, cardiomyopathies, etc..(40)), leading to the absence of benefit or potential harm of exercise prescription. The lack of correspondence between guidelines-based and ventilatory thresholds-based EI domains suggests a shift from a range-based to a ventilatory threshold-based EI prescription to prescribe an appropriate level of intensity associated with proven benefits(11, 12).

In addition, data are also emerging that the VT could be used as a prognostic indicator in cardiac patients for sudden cardiac death, fatal CHD, fatal CVD, and all-cause mortality (41). As a result, in case of a lack of maximal effort during CPET, leading to underestimation of VO_{2peak}, clinicians could still predict mid-to-long-term clinical outcomes by determining the VT. Notably, we recommend performing an “unloaded pedaling” of 2-3 minutes to significantly improves the ability to determine VT_1, especially in highly deconditioned patients.

The exercise prescription

The exercise prescription bases its principles on the so-called "FITT" model, which takes into account the following data in the training programs(3, 12, 42):

- *Frequency*, i.e. the number of sessions per week
- *Intensity*, the amount of energy expenditure during training sessions
- *Time*, the duration of training sessions and the entire program

- ➢ *Type* of exercise, e.g. aerobic exercise, resistance training, balance and flexibility, stretching…

Key recommendations to adequately prescribe exercise in a patient with heart disease are summarized in Table 1.

How to define the intensity of aerobic exercise.

As moderate-intensity aerobic exercise should be commonly prescribed in cardiac patients, the determination of EI is a key concept for an appropriate prescription, being directly related to both the improvement of functional capacity and the risk of adverse events during physical activity(25). EI is commonly expressed for the patient as determined by the HR to be maintained during the exercise. In particular, the light-to-moderate exercise domain encompasses all WRs engendering steady-state VO_2 values below that corresponding to the VT_1(25). Moderate-to-high EI comprises those WRs lying between the VT_1 and the so-called 'critical power' (CP), that is, the upper limit of prolonged aerobic performance above VT_1 in normal subjects, that is, the highest power sustainable in conditions of both $VO_2$and lactate steady state(25, 43). High-to-severe EI comprises all the WRs above CP that cause VO_2 to reach its peak value with no steady-state attainment(25, 43).

The recent ESC guidelines for sports cardiology and exercise and the previous recommendations propose a classification of EI based on different objective or subjective parameters(Figure 2)(3, 25). An indirect quantification method of energy expenditure is represented by subjective parameters, quantifiable by a numerical scale (known as the "Borg Scale"), which corresponds to fatigue during the effort. Although it presents the limits of a completely subjective indicator, the Borg Scale allows determining practically and immediately the EI(13). Among subjective measurements to assess the intensity of exercise, the "talk test" can also be used. According to this test, moderate EI can be

achieved when a subject can speak quite easily during the exercise despite increased ventilation. At the same time, vigorous activity corresponds to an intensity that makes it hard to talk because of the increase in frequency and depth of breathing. However, EI can be better defined by objective measures, particularly by the determination of VTs, which can then be complemented by Borg RPE (12). The objective parameters proposed by the current guidelines include the percentage of VO_{2peak} ($\%VO_{2peak}$) and the percentage of HR_{peak} ($\%HR_{peak}$). Both these data can be obtained during CPET, which, compared to the ranges established *a priori* by the guidelines, provides the advantage of precisely defining the percentages of VO_{2peak} and HR_{peak} corresponding to the VTs, which, in turn, correspond to precise levels of intensity and therefore allow for an exercise prescription that is more compliant with the individual profile. The percentage of HR_{peak} is commonly used to prescribe exercise, and the intensity is determined indirectly through regression equations or tables and is represented by a range of percentages of HR_{peak} (i.e. 55-74% of HR_{peak} for moderate intensity) indirectly corresponding to the percentage of VO_{2peak}(3, 25, 44). Another parameter recommended to define EI is the percentage of HR reserve (% HRR), defined as the difference between the HR at peak and HR at rest. The %HRR is closely related to the percentage of VO_2 reserve ($\%VO_2R$), reflecting the actual energy expenditure, taking into account the basal value at rest(25). Consequently, the %HRR was adopted in the past as the gold standard for the indirect determination of EI. Depending on the level of endurance training, a range between 40 and 60% of %HRR was identified as coincident with VT_1, and it corresponds to moderate intensity(3, 45). However, a loss of linearity of both the VO_2 versus work and heart rate versus work relationships, as peak VO_2 is approached, has been described in the HF population(44). Moreover, chronotropic incompetence can be present in cardiac patients due to age-, pathology- and/or drug (beta-blockers)-related sinus node dysfunction(44). Therefore, the $\%VO_2R$ estimated reliability based on %HRR in these patients is uncertain(44). The main limitation of these methods is that they do not consider the actual

correspondence of the prescribed intensity with the individual values of VTS. The classification of the current recommendations has been formulated based on the predicted values in populations of sedentary healthy subjects or even in competitive athletes, and it allows identifying a $\%HR_{peak}$ that ideally corresponds to a moderate (i.e., corresponding to the VT_1) or vigorous EI (corresponding to the VT_2)(11, 25). However, these percentage values are difficult to adapt to cardiac patients, and the cut-offs estimated for the general population and athletes do not have an actual correspondence in cardiac patients in which the intensity should be defined through an objective and tailored quantification, i.e., through the identification of VTs (11). Indeed, cardiac patients often have different rates of transition to aerobic metabolism - due, for example, to ventilation, cardiovascular or muscular abnormalities, to the drugs taken or deconditioning - and VTs can be identified at levels of exercise different from healthy subjects, even with the same VO_{2peak} and HR_{peak}(8, 11). Therefore, the ranges established by the current guidelines may differ significantly from the individual physiological response to exercise. In cardiac patients, the percentage values measured at VT_1 may correspond even to vigorous EI, underlying that the prescription of training programs in these patients should not ignore the objectification of energy expenditure through CPET(8), which gives us the unique opportunity to obtain the VTs, crucial for a personalized exercise prescription. Subsequent studies confirm these worries(7, 9, 11). As a result, the ranges of EI defined by the current guidelines do not consider the individual variability of the VTs, whose correspondence with the presumed intensity levels may not be optimal, especially in patients whose thresholds are altered by clinical or pharmacological factors by detraining(11). Consequently, prescribing EI based on derived percentages rather than individually determined VTs could result in an over-or under-estimation of exercise intensities, leading the patient to train at an EI level different from that shown to have a distinct clinical benefit(11). Therefore, the prescription of

training programs based on VTs represents the best method to optimize physical exercise on the patient's characteristics.

Conclusions

Physical activity and structured exercise are therapy with proven efficacy for primary and secondary prevention of cardiovascular diseases. The essential requirement for the patient to benefit from physical activity is based on a personalized exercise prescription that takes the patient's clinical, individual and pharmacological characteristics into account. The CPET represents a precious clinical tool for risk stratification maximal exercise capacity and energy metabolism during exercise, e.g., ventilatory thresholds. These parameters facilitate personalized prescriptions of corridors of aerobic and anaerobic EI. Moreover, these data objectify changes induced during medical therapy or exercise intervention. Therefore, CPET should be more commonly used in routine cardiology.

FIGURE LEGEND

Figure 1. Cardiopulmonary exercise testing and 9-panel representation of the data.

VO_2: oxygen consumption; VCO_2: carbon dioxide production; HR: heart rate; VE: minute ventilation; Pet: partial pressure of end-tidal; RER: respiratory exchange ratio; VC: current volume; CV: vital capacity; CI: inspiratory capacity; MVV: maximal voluntary ventilation

Figure 2. Triphasic model proposed by Skinner et al. (23). with the parameters useful to define exercise intensities. Modified by Binder et al. (22) and the recent ESC guidelines(3).

VO2: oxygen consumption; HR, heart rate; HRR, heart rate reserve; VO_2R: VO_2 reserve.

Figure 3. Methods to determine the first and second ventilatory thresholds by cardiopulmonary exercise test**.**

VO_2: oxygen consumption; VCO_2: carbon dioxide production; VT1: first ventilatory threshold; VT_2: second ventilatory threshold; VE: minute ventilation; Pet: partial pressure of end-tidal

Figure 4. Case presentation of a 55-year-old male patient with ischemic cardiomyopathy with severely reduced ejection fraction (EF: 20%), ICD implantation (ATP 180 bpm, VF zone 220 bpm). VO_{2peak} at start of cardiac rehabilitation (CR) 20 ml/min/kg (65% of predicted). ***Panel 1:*** moderate intensity continuous training (MICT) on a bicycle ergometer. Intensity tailored based on ventilatory thresholds (VT) of a CPET at CR start. A) start of CR; B) Progression after 6 weeks of MICT. ***Panel 2:*** High intensity interval training (HIIT). Intensity tailored based on ventilatory thresholds (VT) of a CPET after 6 weeks of CR. High intensity training zone above VT_2, low intensity below VT_1. C) First HIIT; D) Progression after 6 weeks of HIIT. ***Panel 3:*** Progression of cardiorespiratory fitness over 12 weeks CR program. After 6 weeks MICT, VO_{2peak} +2.8 ml/min/kg, 14%; after additional 6 weeks HIIT, VO_{2peak} +5.0 ml/min/kg, 25%.

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